REMARKS

Claims 1-4 and 6-11 are pending the in application, with claim 5 being cancelled, claims 1, 7 and 11 being amended and claims 8-10 being withdrawn.

Objections to the claims

Claims 7 and 11 have been objected to for encompassing non-elected subject matter. Claims 7 and 11 have been amended to be drawn solely to SEQ ID NO:1.

Rejections under 35 U.S.C.§101

Claim 11 has been rejected as being drawn to non-statutory subject matter for encompassing a product of nature. Claim 11 has been amended to be drawn to an "isolated" gene.

Claim 11 has been further rejected for failing to be supported by a substantial established utility. As a first point in the rejection, the Examiner notes that the specification does not show that SEQ ID NO:1 is differentially up-regulated by glucose. As a second point, the Examiner asserts that the art (specifically Girard et al.) teaches that differential expression of a gene in the presence of glucose does not necessarily mean that the gene is involved with the presentation of diabetic nephropathy. Claim 11

has similarly been rejected under 35 U.S.C.§112, first paragraph for lack of enablement with the assertion that one skilled in the art would not know how to use the invention. The basis for this rejection is the same as that under 35 U.S.C.§101. Applicants traverse these rejections and withdrawal thereof.

With regard to the Examiner's first point, i.e. that the specification does not show that SEQ ID NO:1 is up-regulated by glucose, attached hereto is a declaration submitted under 37 C.F.R.§1.132 with experimental data showing the differential up-regulation of SEQ ID NO:1 in the presence of glucose. See Part I of the declaration wherein it is shown in Figure 1, using PCR analysis that the expression of IHG-1 (SEQ ID NO:1) in mesangial cells increases by a factor of 29 when cultured with 30 mM glucose, compared to the normal 5 mM glucose concentration. Thus, as presumed by the Examiner, SEQ ID NO:1 is differentially expressed in the presence of glucose.

With regard to the Examiner's second point, i.e. that a gene that responds to glucose it not necessary involved with the presentation of diabetic nephropathy, the Examiner has applied an incorrect legal standard for evaluating the asserted utility of the invention. The Examiner himself states that the field of the invention accepts that "the propagation of mesangial cells under conditions of high ambient glucose has provided a useful *in vitro*

model with which to probe the molecular basis for mesangial accumulation." The Examiner further states that the art "teaches that the pathological hallmark of diabetic nephropathy is glomerulososclerosis due to accumulation of extracellular matrix."

The present application is directly analogous to the situation in In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995). Similarly in Brana the examiner found a claimed compound failed to meet an asserted utility based on *in vitro* testing. The Federal Circuit in Brana stated,

> The references cited by the Board, Pazdur and Martin, do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility.

The Examiner appears to have made a similar rejection in the present application, i.e. asserting the claimed compound (SEQ ID NO:1) for a lack of utility based on a reference that questions the therapeutic predictive value of the *in* vivo test used by the applicants. The court further stated in Brana that such a rejection is improper and that

> Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. **We hold as we do because it is our firm conviction that one who has taught the public that a**

compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. (emphasis added).

As noted above, the Examiner himself acknowledges that the test used by Applicants is accepted in the art as "a useful *in vitro* model with which to probe the molecular basis for mesangial accumulation." Thus, Applicants have sufficiently shown a utility for the invention of claim 11 and the rejection is improper.

In addition, it has been shown experimentally that SEQ ID NO:1 (IHG-1) is involved with diabetic nephropathy. Attached hereto as Exhibit A is a poster abstract from Murphy et al., meeting of the American Society of Nephrology, November 14, 2003, Poster/Abstract No. F-PO294. The poster abstract reports that IHG-1 (SEQ ID NO:1) expression is elevated in renal bioposies from patients with nephropathy, compared to controls. In addition, the poster abstract reports that when IHG-1 (SEQ ID NO:1) is over-expressed in an experimental model system the cellular responses to TGF-β are amplified. This finding is significant because TGF-β is recognized in the field of the invention as being a major molecular driver of diabetic nephropathy progression.

As described in Part II of the declaration, the protein encoded by SEQ ID NO:1 (IGH-1) shows a characteristic cellular

distribution in mesangial cells and other mammalian cells. The protein encoded by SEQ ID NO:1 specifically associates with the mitochondria. See Figure 2 of the declaration. It is well accepted in the art that the major molecular mechanism for diabetic nephropathy progression is the production of reactive oxygen species in mitochondria of mesangial cells.

Thus, it has been shown that SEQ ID NO:1 is involved with diabetic nephropathy and the asserted utility of claim 11 is credible and substantiated. As such, withdrawal of the rejections under 35 U.S.C.§101 and §112, 1st paragraph is respectfully requested.

Rejections under 35 U.S.C.§112, 2nd paragraph

Claims 1-7 and 11 have been rejected under 35 U.S.C.§112, 2nd paragraph as being indefinite. Specifically, claim 1 has been rejected as being unclear in the recitation of "having a role." The Examiner further rejects claim 1 with the suggestion that the claim should more clearly state that genes are being identified in the recited method that "may" have a role in the presentation of diabetic nephropathy. Claim 1 has been amended as suggested by the Examiner, to state, "A method for identifying a gene ~~having a role in~~ **which may be involved with** the presentation of diabetic

nephropathy." Withdrawal of the rejection is respectfully requested.

Claim 11 has also been rejected as being indefinite for being drawn to a product whereas claim 7 is directed to a method. Claim 11 has been amended to be in independent form. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C.§102

Claims 1-3 have been rejected under 35 U.S.C.§102(b) as being anticipated by Murphy et al. (1998). Claim 1 has been amended to incorporate the subject matter of non-rejected claim 5. As such, withdrawal of the rejection is respectfully requested.

If there are any questions with regard to the present response or other issues in the application, the Examiner is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area, at (703) 205-8000.

Applicants request a three (3) month extension of time for filing the present response. The required fee is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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MAA/
1377-0170P

Attachments: Declaration under 37 C.F.R. §1.132
Exhibit A

Exhibit A

[F-PO294] IHG-1 Enhances TGF-Beta-Induced Transcriptional Activation and Its Expression Is Increased in Diabetic Nephropathy

Madeline Murphy, Dermot Curtin, Vincent Dolan, Carmel Hensey, Matthias Kretzler, Detlef Schlondorff, Catherine Godson, Hugh R. Brady, Finian Martin. Conway Institute of Biomolecular and Biomedical Research, Departments of Medicine and Therapeutics and Pharmacology, University College Dublin, Dublin, Ireland; University of Munich,
Munich, Germany.

Using a PCR based subtractive technique, suppression subtractive hybridization, we have identified a novel gene, increased in high glucose-1 (IHG-1) to be induced by high glucose in cultured human mesangial cells. Culture of mesangial cells in high ambient glucose is a useful in vitro model with which to study disease progression in DN. Increased expression of IHG-1 in this model was confirmed by northern blot analysis. IHG-1 RNA levels were also shown to be significantly increased in renal biopsies taken from patients suffering from DN as compared to those taken from normal kidneys using real time PCR analysis. IHG-1 is identical to an uncharacterised sequence (FLJ20546) of 2263bp encoding a hypothetical protein of 298 amino acids (Genbank # NM_017872, Unigene HS 353090). The IHG-1 putative protein is highly conserved throughout evolution, with homologues being found in mice, drosophila, plants, yeast and bacteria. While this evolutionary conservation suggested an important functional role, there was no known function associated with any of the protein homologues. In mammalian cells IHG-1 enhanced TGF- beta1 mediated transcription of a transfected reporter gene and mediated its effects, at least in part, through
modulation of the Smad signal transduction pathway.shown. IHG-1 also enhanced Smad 3 mediated reporter gene expression Overexpression of IHG-1 in Xenopus embryos resulted in a spina bifida phenotype similar to that induced by the TGF-beta regulator, Xsmad7. Thus IHG-1 is an evolutionary highly conserved protein, a potentially novel modulator of TGF-beta signalling and a DN-associated transcript.

Friday, November 14, 2003 10:00 AM

Poster: Growth Factors and Signaling in Diabetic Nephropathy (10:00 AM-12:00 PM) Poster Board Number: F-PO294